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Treatment of vaginal candidosis with econazole nitrate and nystatin

A comparative study

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SUMMARY A study carried out to compare the efficacy of econazole nitrate and nystatin in the treatment of vaginal candidosis showed that a three-day course of econazole nitrate pessaries was as effective as a 14-day course of nystatin pessaries and is more acceptable to patients.

Introduction

Infection of the vagina with *Candida albicans* is a common condition.[1-3] Most women respond well to topical medication, although patient compliance can be a problem[4] and relapse is common.[5] Short-term therapy requiring the minimum of co-operation from the patient has advantages, and to this end imidazole analogues were developed as antifungal agents.

Econazole nitrate (Gynopevaryl, Ortho Pharmaceutical Ltd, High Wycombe, Bucks) is a new broad-spectrum antimycotic agent, which has been shown to be effective against dermatophytes, yeasts, and Gram-positive bacteria[6]; reports of clinical studies of the treatment of vaginal candidosis have indicated cure rates of about 93%.[7]

Obtaining adequate follow-up data for studies of vaginal candidosis, particularly with patients seen at departments of genitourinary medicine, is always difficult. Poor attendance rates for follow-up visits can introduce an adverse bias in the calculation of cure rates, since the women whose conditions have been cured are less likely to return to the clinic than those whose problems persist. This study was designed to investigate the relative efficacy of econazole nitrate in the treatment of vaginal candidosis by comparing cure rates with econazole nitrate with those with nystatin pessaries (Nystan, E R Squibb & Sons Ltd, Twickenham, Middlesex), the standard therapy.

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Patients and methods

STUDY POPULATION

The patients studied were 224 non-pregnant women attending the department of genitourinary medicine at the Middlesex Hospital, London. All had clinical signs and symptoms of vaginal candidosis including vaginal discharge, irritation, and redness. Only patients with positive vaginal culture results for *C albicans* were included in the study. Patients with concomitant infection due to *Neisseria gonorrhoeae* or *Trichomonas vaginalis* were excluded, as were patients with a history of sensitivity to imidazole derivatives.

CLINICAL HISTORY

A history was taken of age, previous episodes of vaginitis, current methods of contraception, other concomitant medication, and family history of diabetes mellitus. Patients were asked about the presence of vaginal discharge, vulval or perineal pruritus, dyspareunia, and dysuria. Findings relevant to the diagnosis of vaginal candidosis, such as vaginal discharge, vulvitis, and vaginitis, were recorded.

CULTURE AND MICROSCOPY

Neisseria gonorrhoeae

Urethral and cervical smears were stained by Gram's method and examined for the presence of Gram-negative intracellular diplococci. Cultures for *N gonorrhoeae* were taken from the cervix and urethra on non-selective Columbia blood agar medium.

Trichomonas vaginalis and yeasts

Wet vaginal smears were examined by darkground

microscopy for trichomonads. Vaginal smears were stained by Gram's method and examined for yeasts. Material from the vagina was cultured on Sabouraud's medium (Oxoid) for *C albicans* and in Feinberg-Whittington medium for *T vaginalis*.

TREATMENT GROUPS

Patients were allocated according to a random code to one of two treatment groups. One group (group 1) was given three econazole nitrate 150-mg pessaries and instructed to insert one pessary high into the vagina for three consecutive nights. The other group (group 2) was given 28 nystatin pessaries (100 000 units per tablet) with instructions to insert two pessaries into the vagina for 14 consecutive nights. Written directions for the use of the medication was given to each woman; these stressed the need for compliance and instructed patients to continue treatment regardless of menstruation.

FOLLOW-UP

The first follow-up visit took place one week after the end of treatment and subsequent visits at six and 12 weeks after enrolment. Patients were asked whether they had taken any additional medication or changed their existing medication, in particular hormonal oral contraceptives; if they had, they were excluded from the study.

At each follow-up visit the patient was questioned about her symptoms, and tests for *C albicans* and *T vaginalis* were repeated as already described.

STATISTICAL ANALYSIS

The χ^2 test with Yates's correction was used.

Results

Of the 224 patients enrolled into the study, 120 were given econazole nitrate (group 1) and 104 nystatin (group 2). Forty-three patients in group 2 and 35 in group 1 were subsequently excluded from the study, which left 146 records suitable for analysis. The reasons for exclusion are summarised in table I; the commonest was failure to return to the clinic for follow-up. Both groups were very similar for age, incidence of previous vaginal infection, and use of oral contraceptives (table II).

TABLE I *Number of patients enrolled and excluded from two treatment groups: group 1 treated with econazole nitrate pessaries and group 2 with nystatin pessaries*

	Group 1	*Group 2*
Total No enrolled	120	104
Defaulted (% of total enrolled)	22 (18)	36 (35)
Culture-negative for *C albicans* at initial visit	5	1
Concomitant vaginal infection with *T vaginalis* or *N gonorrhoeae*	3	3
Other therapy used	5	3
Total excluded from study (%)	35 (29)	43 (41)
Total included in study	85	61

TABLE II *Demographic data of two treatment groups: group 1 treated with econazole nitrate pessaries and group 2 with nystatin pessaries*

	Group 1 (n-85)	*Group 2 (n-61)*
Mean age (years) ±SEM	25±0·51	25±0·62
Previous candidosis (within last 12 months)	35 (41·2%)	25 (40·9%)
Taking oral contraceptives	46 (54%)	36 (59%)

SEM = Standard error of mean

CULTURAL

Eighty-five per cent of the patients in the econazole nitrate group (group 1) and 92% of patients in the nystatin group (group 2) had negative culture results for *C albicans* at the first follow-up visit (table III). This difference was not statistically significant ($\chi^2_1 = 1·06$; $0·5 > P > 0·3$). Of the 33 patients in group 1 who returned for their second follow-up visit, nine had positive culture results; eight of these had had negative results at their first follow-up visit, so the return of *C albicans* represented a relapse or re-infection. In group 2, seven patients were found to have relapsed or to have been reinfected at their second follow-up visit. This difference was not significant ($\chi^2_1 = 0·001$; $1·0 > P > 0·9$).

TABLE III *Results of culture and microscopy for Candida albicans in two treatment groups: group 1 treated with econazole nitrate pessaries, group 2 with nystatin pessaries*

			Follow-up visits					
	Initial visit		*1st*		*2nd*		*3rd*	
C albicans present	*Group 1 (n = 85)*	*Group 2 (n = 61)*	*Group 1 (n = 85)*	*Group 2 (n = 61)*	*Group 1 (n = 33)*	*Group 2 (n = 26)*	*Group 1 (n = 10)*	*Group 2 (n = 12)*
Culture (%)	85 (100)	61 (100)	13 (15)	5 (8)	9 (27)	7 (27)	0	1
Microscopy (%)	74 (87)	44 (72)	5 (6)	2 (3)	2 (6)	2 (8)	0	0

CLINICAL

The results of local treatment in the two groups are shown in table IV. About 75% of the women in each group presented initially with excessive vaginal discharge (as observed by the physician and reported by the patient) and pruritus. Vulvitis and vaginitis were less commonly observed and occurred in about half the patients. Vaginal discharge (as observed by the physician) was still present in 33% of the women treated with econozole nitrate and in 25% of those treated with nystatin at their first follow-up visit. Vaginal discharge as a symptom persisted in 16% of group 2 and in 29% of group 1. This difference was not significant ($\chi_1^2 = 2 \cdot 63$; $0 \cdot 2 > P > 0 \cdot 1$) nor was the difference between groups for the incidence of pruritus ($\chi_1^2 = 0 \cdot 71$; $0 \cdot 5 > P > 0 \cdot 3$). The fact that women from group 1 returned for follow-up 10 days after the start of therapy and those in group 2 three weeks after the start of therapy should also be considered when the results of the changes in symptoms are interpreted.

A rise in the percentage incidence of clinical signs and symptoms was recorded at the second compared with the first follow-up visit, probably because of the problems of the relapsed and reinfected patients.

The number of women who returned for their third follow-up visit was very small and few valid comments can be made on the findings.

PATIENTS' COMMENTS

Any comments made spontaneously by the women were recorded at each follow-up visit. Such anecdotal information is very difficult to summarise but could be roughly classed as adverse or favourable. For nystatin treatment three favourable comments were made, ranging in enthusiasm from "not unpleasant" to "helped a lot." Ten women complained that they were messy, three found them difficult to insert, and three objected to the length of treatment. Thirteen women treated with econazole nitrate made favourable comments, mainly about the ease of insertion, shortness of treatment, and efficacy of cure. Nine patients remarked that some soreness persisted after the completion of econazole nitrate therapy. However, this finding should again be considered in the light of the different timings in follow-up between the two treatment groups.

Discussion

If large numbers of patients default from a clinical study, the interpretation of results becomes very difficult. About 35% of the patients enrolled in this study failed to return for follow-up evaluation. However, the inclusion of a control group treated with standard nystatin therapy has allowed comment to be made on the relative efficacy of econazole nitrate.

Nystatin treatment, consisting of 200 000 units (two tablets) for 14 days showed no superiority over 15-mg pessaries of econazole nitrate treatment for three days in either cure rate or relief of signs and symptoms.

The problem of patient compliance has previously been mentioned and treatment completed within three days probably offers an advantage, since there is more chance that patients will successfully complete a short course of treatment. Comments on the acceptability of the two vaginal products highlights the importance of presentation. The nystatin pessary is a dry compressed tablet, which can cause discomfort when inserted into an inflamed vagina and, when dissolved, can produce leakage. About one-quarter of the patients treated with nystatin complained spontaneously about these problems.

TABLE IV *Effect of treatment on relief of symptoms and signs of infection in two treatment groups: group 1 treated with econazole nitrate pessaries, group 2 with nystatin pessaries (results expressed in percentages)*

	Initial visit		*Follow-up visits*					
			1st		*2nd*		*3rd**	
	Group 1 (n = 85)	*Group 2 (n = 61)*	*Group 1 (n = 85)*	*Group 2 (n = 61)*	*Group 1 (n = 33)*	*Group 2 (n = 26)*	*Group 1 (n = 10)*	*Group 2 (n = 12)*
Symptoms								
Discharge	67	75	29	16	36	25	(3)	(4)
Pruritus	76	80	23	16	33	31	(1)	(2)
Dyspareunia	29	41	12	10	15	8	0	(1)
Dysuria	27	25	8	5	3	11	0	(1)
Signs								
Discharge	75	74	33	25	42	42	(5)	(3)
Vulvitis	43	46	11	8	6	11	(1)	(1)
Vaginitis	48	44	11	6	6	15	0	(1)

*The number of patients reporting for the third follow-up visit was small and results are given in absolute numbers

Econazole is formulated in a wax-like pessary base and favourable comments were made on the ease of insertion and the lack of leakage.

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